Endothelin-1 inhibitors in chronic pancreatitis

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Fibrosis is a key feature of chronic pancreatitis and pancreatic cancer. The extensive deposition of extracellular matrix proteins fosters the development of an exocrine and endocrine organ insufficiency, and accelerates progression of the tumour. Pancreatic stellate cells (PSC) are the principal effector cells in pancreatic fibrosis. They are activated by profibrogenic mediators, which include, for example, cytokines and ethanol metabolites. So far, there are no therapies available to interfere with fibrogenesis in the diseased organ.

A better understanding of the cellular and molecular mechanisms of PSC activation represents an important prerequisite for the development of novel therapeutic approaches aimed at the treatment of pancreatic fibrosis in the context of inflammation and cancer.

A research article to be published on September 7, 2009 in the *World Journal of Gastroenterology* addresses this question. The results of the study by Jonitz et al. provide insights into the effects of the extracellular mediator endothelin-1 (ET-1) in PSC. They indicate that ET-1 stimulates activation of the cells, thereby promoting fibrosis. At the molecular level, the authors have identified molecules (ERK1/2, p38 and AP-1) that mediate the ET-1 signal, and linked them to the process of stellate cell activation. Furthermore, the two proinflammatory cytokines interleukin-1β and interleukin-6 were found to be expressed in ET-1-treated PSC, suggesting, for the first time, a direct link between inflammation and fibrosis at the level of ET-1 action.

In addition, studies on the regulation of ET-1 synthesis revealed that transforming growth factor-β1 and tumour necrosis factor-α strongly stimulate ET-1 secretion by PSC. Together, the results of the study by Jonitz et al. suggest that ET-1 is part of a network of proinflammatory and profibrogenic mediators that fosters interactions between inflammatory cells and PSC, ultimately enhancing inflammation and fibrosis. The authors suggest further experimental studies to elucidate the efficiency of endothelin receptor antagonists in pancreatic fibrosis.

The prognosis of pancreatic cancer is the worst of any common human tumour. Chronic pancreatitis is a disease with limited therapeutic options in a significant proportion of patients, and also represents a risk factor of pancreatic cancer. Inhibition of accompanying fibrosis might become a novel adjuvant approach to treat both diseases in the future, once specific antifibrotic agents become available.

More information: Jonitz A, Fitzner B, Jaster R. Molecular determinants of the profibrogenic effects of endothelin-1 in pancreatic stellate cells. *World J Gastroenterol* 2009; 15(33): 4143-4149
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